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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,622	06/27/2005	Giulio Alessandri	47706	2850

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ROYLANCE, ABRAMS, BERDO & GOODMAN, L.L.P.
1300 19TH STREET, N.W.
SUITE 600
WASHINGTON,, DC 20036

EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	PAPER NUMBER
1651	
MAIL DATE	DELIVERY MODE
05/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,622	ALESSANDRI ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2008 and 17 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *3-6 and 10-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 7-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 2/17/09 and 12/18/08 have been entered.

Claims 1-14 as recited in the listing provided 6/26/08 are currently pending. Claims 3-6 and 10-14 remain withdrawn pursuant to the restriction requirement. Claims 1, 2, and 7-9 are being examined on their merits.

Claim Objections

Claim 9 is objected to because of the following informalities: The designation of process steps by letter does not appear to correspond with that in claim 8. Appropriate correction is requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, and 7-9 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

The claims are drawn to a method of making stem cells by preparing a suspension of cells from human adipose tissue and culturing the cells in a medium comprising bovine serum albumin (BSA), four growth factors (bFGF, EGF, VEGF, and LIF), heparin, and other components. In some dependent claims, the amounts of components added to the media are particularly pointed out. In some dependent claims, the cells are incubated on a collagen-coated culture dish and then on a non-coated dish.

Adipose stromal cells were known at the time of the invention to be a source of stem cells. Zuk et al. (2002, *Molecular Biology of the Cell* 13: 4279-4295; IDS) teach washing lipoaspirate with PBS, treating said lipoaspirate with collagenase, and culturing the cells freed by the collagenase action in DMEM supplemented with FBS (page 4280 and Table 1).

Adding growth factors and other active agents to cultures of primary cells isolated from adipose is known to alter the differentiation state of the cells. Hauner et al. (2001, *Methods in Molecular Biology* 155: 239-247; IDS) teach that culturing cells dissociated from adipose tissue in medium comprising insulin promotes differentiation of the cells to adipocytes (page 243, section 3.6, item 2). Hauner (2001) further teaches that incubating adipose stromal cells with FGF promotes adipocyte differentiation (page 243, section 3.5). Hauner et al. (1995, *European Journal of Clinical Investigation* 25: 90-96; IDS) teaches that EGF modulates the differentiation state of primary adipocyte precursor cells (page 90, column 2). Zhao et al. (1997, *Journal of Steroid Biochemistry and Molecular Biology* 61: 203-210) teach that LIF induces adipose stromal cells to begin synthesizing estrogen *in vitro* (Abstract and page 204, column 2). Amri et al. (1986, *Biochemical Journal* 238: 115-122) teach that putrescine promotes differentiation of adipose stromal cells to mature adipocytes (Abstract and Figure 1, e.g.). Investigations published after the instant filing indicate that the skilled artisan would not have had a reasonable expectation of using the instantly recited method to yield stem cells from adipose. Song et al. (2007, *Biochemical and Biophysical Research Communications* 354: 999-1003) teach that adipose stromal cells cultured in VEGF spontaneously differentiate into cardiomyocytes (Abstract and page 1003, column 1).

At the time of the invention, skilled artisans recognized that the particular composition of the medium in which adipose stromal cells are cultured affects the differentiation state of the cells. However, the effect of a particular active agent added to the medium in which stromal cells are cultured on the differentiation state of the cells

was not predictable at the time of the invention. The guidance in the specification provides insufficient evidence that the skilled artisan would have reasonably expected to obtain stem cells that retain the ability to differentiate into nerve cells, vascular cells, and bone cells from adipose tissue. The specification describes the properties of cells obtained using the instantly claimed steps on muscle tissue, but the working examples include no characterization of cells obtained from adipose tissue.

M.P.E.P. § 2164.03 reads, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The 'amount of guidance or direction' refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. **In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.** See, *e.g., Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004)…In applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required." As the above discussion illustrates, the effects of at least a few active agents

on adipose stromal cells were unpredictable at the time of the invention, so addition of any given active agent or combination thereof to adipose stromal cells must be considered "nascent," and the amount of guidance required is relatively high.

The specification reads, "Because the [human fat stem cells] of the present invention are of the same mesenchymal origin as the [human muscle stem cells], this also suggests that the same differentiating abilities described above contained in the hMSC are also present in the hFSC" (page 11, paragraph 5). However, this statement is not supported by evidence. Numerous diverse tissues including connective tissue, bone, cartilage, and blood, as well as the tissues that make up the circulatory and lymphatic systems, arise from mesenchyme. These tissues do not share functions with each other or with adipose and/or skeletal muscle, and they do not contain the same kinds of cells. The specification provides no evidence that all tissues of mesenchymal origin may be cultured in the instantly claimed culture medium to yield undifferentiated stem cells.

It is noted that applicant has supplied experimental evidence regarding the multipotency of cells yielded by a method encompassed by the instant claims (see declaration under 37 C.F.R. 1.132 by inventor Giulio Alessandri, submitted 12/18/08). The term "stem cell" is not completely synonymous with "precursor cell" or "progenitor cell." By definition, a stem cell is capable of both differentiation and self-renewal (see, e.g., Carlino, 1995, U.S. Patent 5,426,098; reference A; at column 4, lines 13-14; and Weiss et al., 1998, U.S. Patent 5,750,376; reference B; at Figure 1 and column 2, line 61, through column 3, line 4). It is this second property that is particularly at issue in this

rejection. Neither the specification nor the declaration by inventor Alessandri provides evidence that the cells yielded by applicants' method are true stem cells, since no evidence of self-renewal ability is provided. At best, applicant's disclosure enables a method of making a multipotent progenitor or precursor cell, but not a stem cell.

While a narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the lack of direction applicants present, provides additional weight to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention.

Applicant has supplied a declaration by inventor Giulio Alessandri (hereinafter "the Alessandri declaration") in support of enablement (see 12/18/08 reply). The evidence in the Alessandri declaration has been fully considered, but it is not persuasive.

As discussed in the rejection, the Alessandri declaration includes no evidence that the cells isolated from adipose tissue (the "human fat stem cells" of the declaration; see page 2) are truly stem cells, because the declaration is silent as to the key self-renewal property of stem cells. The references cited by the examiner establish that at the time of the invention, the skilled artisan would have reasonably expected that incubating cells in growth factors would modulate their differentiation state, and the Alessandri declaration does not provide insight into the cells' ability to self-renew.

It is further noted that the HUMAN-G medium described at page 7 of the specification and referenced in the working examples and the Alessandri declaration is

not commensurate in scope with the medium employed in the instant method. For example, the instant claims do not require that the medium comprise putrescine or progesterone.

For at least these reasons, the Alessandri declaration is not commensurate in scope with the invention as claimed and does not overcome the rejection of record. See M.P.E.P. § 2164.05.

No claims are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651